Arch. Pharm. Res. **15**(4), 333-335 (1992)

Practical Hofmann Rearrangement

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(Received October 6, 1992)

Abstract □ Hofmann rearrangement of a series of primary aliphatic and aromatic carboxamides **1a-1m** with HgO-NBS (or dibromantin)-R'OH-DMF gives corresponding carbamates **2a-2m** in excellent yields.

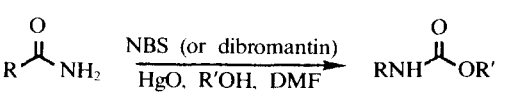
Keywords □ Hofmann rearrangement, carboxamides, HgO, NBS, dibromantin, carbamate.

The Hofmann rearrangement which involves migration to an electron-deficient nitrogen atom accomplishes conversion of primary carboxamides to amines or carbamates possessing one less carbon[1].

A large number of methods for the rearrangement have been developed and these are classified into two groups. The one is the method of using postive halogen, such as NaOBr[1a], CH_3OBr[2], KBr-MeOH (electroorganic process)[3], $NaBrO_2$[4], $C_6H_5CH_2(CH_3)N^+Br^-$-NaOH[5] and NBS-CH_3ONa-DMF[6], the other is that of using two-electron oxidant, such as $Pb(OAc)_4$[7], $C_6H_5I(OCOCF_3)_2$[8], C_6H_5IO[9] and $C_6H_5I(OTs)OH$[10].

Recently a new method using N-bromosuccinimide(NBS)-$Hg(OAc)_2$ and 1,3-dibromo-5,5-dimethylhydantoin(dibromantin)-$Hg(OAc)_2$ in DMF was developed by us. It could transform a series of primary aliphatic and aromatic carboxamides to corresponding carbamates in excellent yields[11], but since the highly toxic BrHgOAc formed from $Hg(OAc)_2$ was dissolved in DMF, its removal was very tedious and difficult. In an effort to improve the method all the more, we attempted to adopt HgO in place of $Hg(OAc)_2$. The mercuric compound, probably BrHgOH produced from HgO was expected to be insoluble in DMF in contrast to BrHgOAc and to be simply and easily removed by filtration.

In this communication, we would like to describe an efficient and practical method for Hofmann rearrangement using NBS (or dibromantin)-HgO-R'OH-DMF.

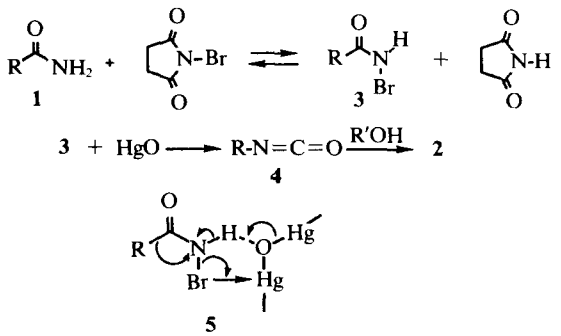


1 2

A typical procedure is as follows: To a reddish orange suspension of cyclohexanecarboxamide **1e** (105 mg, 0.826 mmol), NBS (168 mg, 0.909 mmol) and HgO (201 mg, 0.909 mmol) in 4 m*l* of DMF, MeOH (334 mg, 8.26 mmol) was added at room temperature under argon. The reddish orange suspension was stirred at room temperature for 0.5 hours, when it became orange. Stirring of the mixture was allowed to continue for 11.5 hours to give a whitish yellow suspension and it was filtered to eliminate BrHgOH. The filtrate was diluted with 100 m*l* of EtOAc, washed successively with H_2O (10 m*l*), 5% HCl (10 m*l*), H_2O (10 m*l*), sat. $NaHCO_3$ (10 m*l*) H_2O (10 m*l*), and brine (10 m*l*); dried over anhyd. $MgSO_4$; and evaporated to give white solid. This was purified by silica gel column chromatography (hexane : EtOAc = 5 : 1) to give 130 mg of colorless needles, mp. 74-75℃ (yield 100%). The reactions for the other carboxamides and the other method were performed in a similar manner, and

the results are summarized in Table I.

In connection with the mechanism, $C_6H_5CH_2CONHBr$ **3g** obtained by N-bromination of $C_6H_5CH_2CONH_2$ **1g** by using $NaBrO_2$-AcOH-H_2O[12] was treated with HgO-CH_3OH-DMF, the procedure that only NBS was excluded from our method, to afford $C_6H_5CH_2NHCO_2CH_3$ **2g** in 94% yield. Therefore, it is conceivable that N-bromocarboxamide **3** formed through the heterolytic N-Br bond cleavage of NBS by the help of DMF is transformed to the isocyanate **4** *via* the intermediate **5**, considering that the conversion of isocyanate to carbamate is a well-documented process.



All the carboxamides except **1m** were converted to the corresponding carbamate in excellent yields. Probably BrHgOH which was formed from HgO was insolule in DMF as had been expected. Consequently it could be easily removed by simple filtration. As is evident from the yields given in Table I, there was no difference between NBS and dibromantin.

In conclusion, this method using HgO is expected to be more efficient and convenient than $Hg(OAc)_2$ and it should be noted that it can be applied very practically for the Hofmann rearrangement.

Table I. The conversion of carboxamide 1 to carbamate 2

$RCONH_2$ **1** R	% Yield of NBS	$RNHCO_2R'$ **2**[a,b] dibromantin
a $CH_3(CH_2)_6$	91	96
b $CH_3(CH_2)_8$	97	100
c $CH_3(CH_2)_{14}$	90	94
d $CH_3(CH_2)CH(C_2H_5)$	96	100
e cyclohexyl	97	100
f $(CH_3)_3C$	100	100
g $C_6H_5CH_2$	91	100
h C_6H_5	100	100
i p-$NO_2C_6H_4$	96	100
j o-$EtOC_6H_4$	91	81
k o-MeC_6H_4	100	100
l o-ClC_6H_4	100	100
m 3-pyridyl	63	79

[a]R' are methyl groups except for **2f** ($R'=CH_2C_6H_5$). [b]All products gave satisfactory spectral data. [c]The molar ratio of the reagents is as follows; $RCONH_2$(1.0), NBS(1.3) or dibromantin(1.2), HgO(1.2), and R'OH (10.0). The conversion was performed at room temperature, or 45℃ (in the cases of **1b**, **1c** and **1i**) for 12 hours.

ACKNOWLEDGEMENTS

We thank the Korean Science Foundation for financial support (880306) and Research Center for New Drug Development (1992).

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